

-27-

We Claim:

1. A PEGylated FGF-21 compound comprising an FGF-21 compound covalently attached to at least one PEG molecule, wherein each PEG is attached to the FGF-21
5 compound at a cysteine or lysine amino acid residue and wherein the PEGylated FGF-21 compound has extended time action compared to a non-PEGylated FGF-21 compound.
2. The PEGylated FGF-21 compound of Claim 1 comprising the amino acid sequence as shown in SEQ ID NO:1 covalently attached to a PEG molecule at one or
10 more of the residues selected from the group consisting of lysine at position 56, 59, 69 or 122.
3. The PEGylated FGF-21 compound of Claim 1 comprising the amino acid sequence as shown in SEQ ID NO:1 wherein one or more surface exposed amino acid
15 residues are substituted with a cysteine residue and said cysteine residue is covalently attached to a PEG molecule.
4. The PEGylated FGF-21 compound of Claim 3 wherein said substituted amino acid residue is selected from the group consisting of D25C, D38C, L58C, K59C, P60C,
20 K69C, D79C, H87C, E91C, E101C, D102C, L114C, L116C, K122C, R126C, P130C, P133C, or P140C.
5. The PEGylated FGF-21 compound of Claim 4 wherein said substituted amino acid residue is selected from the group consisting of K59C and K122C.
25
6. The PEGylated FGF-21 compound of Claim 1 which is FGF-21 [Leu118Cys-Ala134Cys] wherein the numbering of amino acids is based on SEQ ID NO:1.
7. The PEGylated FGF-21 compound of Claim 1 wherein said PEG molecule has a
30 molecular weight of about 20,000 to 40,000 daltons.

-28-

8. The PEGylated FGF-21 compound of Claim 2 wherein said PEG molecule has a molecular weight of about 20,000 to 40,000 daltons.

9. The PEGylated FGF-21 compound of Claim 3 wherein said PEG molecule has a
5 molecular weight of about 20,000 to 40,000 daltons.

10. The PEGylated FGF-21 compound of Claim 5 wherein said PEG molecule has a molecular weight of about 20,000 to 40,000 daltons.

10 11. The PEGylated FGF-21 compound of Claim 6 wherein said PEG molecule has a molecular weight of about 20,000 to 40,000 daltons.

12. A pharmaceutical composition useful for treating a patient exhibiting obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia,
15 or metabolic syndrome comprising the following:

- (a) A therapeutically effective amount of the PEGylated FGF-21 compound of Claim 1; and
- (b) An acceptable pharmaceutical carrier.

20 13. A pharmaceutical composition useful for treating a patient exhibiting obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome comprising the following:

- (a) A therapeutically effective amount of the PEGylated FGF-21 compound of Claim 2; and
- 25 (b) An acceptable pharmaceutical carrier.

14. A pharmaceutical composition useful for treating a patient exhibiting obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome comprising the following:

- 30 (a) A therapeutically effective amount of the PEGylated FGF-21 compound of Claim 3; and
- (b) An acceptable pharmaceutical carrier.

-29-

15. A pharmaceutical composition useful for treating a patient exhibiting obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome comprising the following:

- 5 (a) A therapeutically effective amount of the PEGylated FGF-21 compound of Claim 4; and
 (b) An acceptable pharmaceutical carrier.

16. A pharmaceutical composition useful for treating a patient exhibiting obesity,
10 type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome comprising the following:

- (a) A therapeutically effective amount of the PEGylated FGF-21 compound of Claim 6; and
 (b) An acceptable pharmaceutical carrier.

15 17. A method for treating a patient exhibiting obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome comprising administering to said patient in need of such treatment a therapeutically effective amount of the FGF-21 mutein of Claim 1.

20 18. The method of Claim 17 wherein said patient exhibits type 2 diabetes.

19. The method of Claim 17 wherein said patient exhibits obesity.

25 20. The method of Claim 17 wherein said patient exhibits metabolic syndrome.

21. A method for treating a patient exhibiting obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome comprising administering to said patient in need of such treatment a therapeutically
30 effective amount of the FGF-21 mutein of Claim 2.

22. The method of Claim 21 wherein said patient exhibits type II diabetes.

-30-

23. The method of Claim 21 wherein said patient exhibits obesity.

24. The method of Claim 21 wherein said patient exhibits metabolic syndrome.

5

25. A method for treating a patient exhibiting obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome comprising administering to said patient in need of such treatment a therapeutically effective amount of the FGF-21 mutein of Claim 3.

10

26. The method of Claim 25 wherein said patient exhibits type 2 diabetes.

27. The method of Claim 25 wherein said patient exhibits obesity.

15

28. The method of Claim 25 wherein said patient exhibits metabolic syndrome.

29. A method for treating a patient exhibiting obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome comprising administering to said patient in need of such treatment a therapeutically effective amount of the FGF-21 mutein of Claim 4.

20

30. The method of Claim 29 wherein said patient exhibits type 2 diabetes.

31. The method of Claim 29 wherein said patient exhibits obesity.

25

32. The method of Claim 29 wherein said patient exhibits metabolic syndrome.

33. A method for treating a patient exhibiting obesity, type 2 diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome comprising administering to said patient in need of such treatment a therapeutically effective amount of the FGF-21 mutein of Claim 6.

30

-31-

34. The method of Claim 33 wherein said patient exhibits type 2 diabetes.

35. The method of Claim 33 wherein said patient exhibits obesity.

5 36. The method of Claim 33 wherein said patient exhibits metabolic syndrome.

37. The use of a PEGylated FGF-21 compound of any one of Claims 1-6 in
the manufacture of a medicament for the treatment of obesity, type 2 diabetes, insulin
resistance, hyperinsulinemia, glucose intolerance, hyperglycemia, or metabolic syndrome.

10

38. The use of Claim 37 wherein the medicament is used to treat , type 2 diabetes.

39. The use of Claim 37 wherein the medicament is used to treat obesity.

15 40. The use of Claim 37 wherein the medicament is used to treat metabolic
syndrome.